

PATENT SPECIFICATION

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- (21) Application No. 54462/71 (22) Filed 23 Nov. 1971
 (44) Complete Specification published 4 Dec. 1974
 (51) International Classification A61K 21/00 9/04
 (52) Index at acceptance
 A5B 216 21Y 232 23X 23Y 271 272 273 27Y 302 30Y
 350 730 733 734 735 736 73X 750 751 753 756 75Y
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(54) POLYENIC MACROLIDE COMPOSITION

(71) We, JULIUS SCHMID, INC., a corporation organised and existing under the laws of the State of New York, United States of America of 423 West 55th Street, New York, New York 10019, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

THIS INVENTION relates to polyenic macrolide compositions; more particularly, this invention relates to improved encapsulated formulations comprising polyenic macrolide compositions; and to processes for their preparation.

Polyenic macrolides are administered orally for the treatment of prostatic hypertrophy, hypercholesterolemia, acne and other conditions. It has been noted that polyenic macrolides, when so administered, tend to be decomposed (inter alia by fission of the lactone ring) in the acidic environment of the stomach. This not only hinders the achievement of optimum effectiveness of a given dosage of the polyenic macrolide but also can cause gastrointestinal disturbance (such as vomiting and diarrhoea) in the patients. This is particularly the case with hexaene or heptaene macrolides such as candicidin, fungimycin and hamycin.

This invention seeks to overcome the disadvantages hitherto attendant on the oral administration of polyenic macrolides.

According, therefore, to the present invention, there is provided a capsule which contains a multiplicity of beadlets (as herein defined) each containing a composition, comprising (i) a polyenic macrolide, particularly a hexaene or heptaene macrolide, such as candicidin, fungimycin, hamycin, and mediocidin, and (ii) an absorbent material capable of binding the

polyenic macrolide under acidic conditions and releasing the polyenic macrolide under substantially neutral conditions, the weight ratio (i) : (ii) being from 1:2 to 1:8, preferably 1:4

Specifically the absorbent material is preferably capable of binding the polyenic macrolide at a pH from 3 to 5, and preferably capable of releasing the polyenic macrolide at a pH from 6 to 7.

Our British Patent No. 1 186 888 should be consulted for information regarding the discovery, isolation, classification and chemical properties of polyenic macrolides. Specifically, *Candicidin* is described in U.S. Patent No. 2 992 162; "Physician's Desk Reference" 19th Edition (1964); and the "Merck Index of chemicals and Drugs" (7th Edition).

Fungimycin is described in U.S. Patent No. 3 182 004 and the "Merck Index of Chemicals and Drugs" (8th Edition).

Hamycin is described in U.S. Patent No. 3 261 751 and in "Martindale's Extra Pharmacopodia" 25th Edition) published February 1967.

Mediocidin is available from the culture collection at the Institute of Microbiology, Rutgers University.

It will be understood that where a polyenic macrolide described in the art is identical with a specifically named polyenic macrolide, but is known by another name by reason, inter alia, of independent production or production in accompaniment to other antibiotics, the identification of such substances by any such name is intended to cover all such identical macrolides. The weight of polyenic macrolide present in such a capsule is preferably from 25 mg. to 100 mg., though can be from 25 mg. to 200 mg.

The absorbent material present in the composition comprising the polyene macrolide should be one that is non-toxic and

SPECIFICATION ATTENDED - SEE ATTACHED SLIP

pharmaceutically acceptable for oral use. The absorbent material may be either organic or inorganic in character. The inorganic materials are preferably salts or bases of divalent or trivalent metals. Thus the cation portion of the inorganic absorbent material may be a metal such as calcium, aluminium, magnesium, bismuth, or iron, with calcium being the preferred cation. The anion portion of the inorganic absorbent material may be a carbonate, a phosphate, a sulphate, a silicate or a hydroxide, with a carbonate being preferred. Illustrative of inorganic absorbent materials are calcium carbonate, calcium phosphate, hydrated aluminium silicate, aluminium hydroxide, magnesium oxide, magnesium carbonate, magnesium trisilicate, magnesium hydroxide, bismuth subcarbonate and aluminium phosphate. Suitable organic absorbent materials include cellulose derivatives such as sodium carboxy methylcellulose, pectin, starches (e.g. barley, arrowroot), gums (acacia, tragacanth), ion exchange resins (e.g. a polyamine methylene resin). The absorbent material is always present in excess in the composition comprising the polyenic macrolide, this being primarily responsible for ensuring that the disadvantages noted hereinbefore are overcome.

This invention also provides a process for producing a capsule according to the invention, which process comprises blending (i) a polyenic macrolide with (ii) an absorbent material capable of binding the polyenic macrolide under acidic conditions and releasing the polyenic macrolide under substantially neutral conditions such that the weight ratio (i) : (ii) is from 1:2 to 1:8; preparing a multiplicity of beadlets (as herein defined) from the composition so produced; and encapsulating the multiplicity of beadlets so produced to form a dosage unit. Preferably, the dosage unit so formed contains an amount of polyenic macrolide effective to deposit from 1 mg. to 40 mg. of macrolide per kilogram of a host's body weight per day.

As used herein "beadlet" means beads, granules, pilules or any micro solid dose form contained in a capsule, preferably hard shell.

It may be desirable to incorporate a pharmaceutically acceptable acidic material in the polyenic macrolide containing composition, particularly where the pH of the polyenic macrolide is substantially on the alkaline side, to maintain the pH of the composition between 6.5 and 7.5. The inclusion of the acidic material will further increase the tolerability of the polyene by providing a composition having a pH in the neutral range. Thus, in the case of candididin, which has a pH of about 10,

it is desirable to bring the pH down to 6.5 to 7.5 with an acidic material such as potassium phosphate (monobasic). Generally, the ratio of acidic material to candididin used in each unit dose is between about 1:1 to 2:1. Other acidic materials may also be used such as citric acid, lactic acid and glycine.

The active ingredient is preferably formulated so that the beadlets are provided with a sustained release coating, this contributing to overcome the disadvantages noted hereinbefore.

The polyenic macrolides may be compounded with inert ingredients including fillers such as talc, lactose, starch, bentonite and diatomaceous earth.

A suitable procedure for preparing the beadlets is as follows:

In the preparative method, the powdered polyenic macrolide is dispensed, e.g. by dusting, on to a medicinally acceptable core material. Nonpareil seeds are preferably employed and it should be understood that while the nonpareil seeds will be referred to collectively as "core" each such nonpareil seed is in fact a separate core. Adhesion of the polyenic macrolide on the core is accomplished by spraying the core with an adhesive formulation in a non-aqueous solvent. The solvents used may be lower alcohol or halogenated hydrocarbons or mixtures thereof. The criteria for the selection of the solvent is the ease with which the solvent volatilizes and can therefore be removed rapidly without heating.

A typical suitable adhesive formulation comprises a non-aqueous solution containing shellac, polyvinyl pyrrolidone and ethyl alcohol. Other non-aqueous adhesives may be employed such as ethyl cellulose, polyethylene glycol 4000, polyethylene glycol 6000 and sodium carboxy methyl cellulose.

Thus the first step of the method involves spraying of a non-aqueous adhesive solution on the core and the second step involves dusting of the polyenic macrolide onto the sprayed core. The polyenic macrolide which at this stage in the process may be in admixture with the selected absorbent material, e.g. calcium carbonate, is spread onto the core using an atomizer. This procedure is carried out by continuous rotation of the coating pan during the time that the polyenic macrolide formulation is being added. Rotation of the pan is continued until all of the alcohol has been evaporated from the adhesive formulation. Evaporation of the alcohol should not be carried out at an elevated temperature because heat may alter or destroy the activity of the polyenic macrolide. The procedure of adhering the polyenic macrolide

to the core is repeated at least nine times using the adhesive formulation as indicated above. After the last coat has been adhered to the core, the core is air dried at room temperature. The resulting formulation provides a product wherein the polyenic macrolide is gradually released in the gastrointestinal tract in combination with the absorbent material.

- 10 If an enteric coat is desired, an appropriate number of edible enteric coatings are overlaid on the polyenic macrolide-coated core to provide a composition that will be identified hereafter as an "enteric coated" beadlet. The number of enteric coats that will be applied can be varied and obviously a fewer or greater number of coats can be applied to afford the desired modifications in the release characteristics of the formulation.

The enteric coating procedure should be carried out in a non-aqueous system and the enteric coated film forming material may be any one of the conventional materials used for such purposes which are described in the prior arts such as shellac, waxes, fatty acids, fatty alcohols, high molecular weight glycerine esters, film forming polymers, fats or a combination of any of one or more of these coatings. Illustrative of substances that may be used for this purpose is cellulose acetate phthalate with resinous carrier; cellulose acetate phthalate-tolu balsam-shellac; cellulose acetate phthalate with fats and waxes; shellac-castor oil; ammoniated shellac; shellac-stearic acid-tolu balsam; stearic acid-castor oil over shellac-silica gel, cellulose acetate phthalate with or without plasticizer and dusting powder(s); acid phthalates of glucose and fructose, ternary copolymers of styrene, methacrylic acid and butyl half-ester of maleic acid; alkyd resin-unsaturated fatty acids-shellac and polyvinyl acid phthalate.

- The enteric coated film is applied to the beadlets by spraying a solution of the selected film forming material on to the beadlets after which the beadlets are permitted to air dry with continuous rotation of the pan in which they are contained. This procedure is repeated until the selected number of enteric coats have been applied to the beadlets. In general, the coating technique involves using conventional equipment. The coating process involves placing an appropriate number of coated beads in a standard coating pan followed by the addition thereto of a sufficient quantity of the coating composition to wet the beads. The rotation of the pan is continued until all the coating composition has been absorbed by the cores. During the coating operation room temperatures are maintained. After the first coating

operation is completed, the beadlets are air dried and thereafter the remaining coats are applied in a similar manner.

The polyenic macrolide beadlets after enteric coating are then passed through a No. 12 mesh sieve discarding any oversize. Thereafter the beadlets are passed through a No. 16 mesh sieve discarding the undersize. Hard shell capsules are filled with the remaining coated beadlets in the range of 1200 to 1700 microns each in size. The number of beadlets to be incorporated into a single hard shell capsule is a variable that is determined by the levels of active ingredients which are desired in the final product. The number of beadlets needed to achieve such level will depend upon the amount of medicine present in the individual beadlets.

Generally, a sufficient number of beadlets are added to the capsule to provide a unit dosage containing from about 25 to 200 mg of polyenic macrolide.

The following examples illustrate the pharmaceutical formulations of the present invention:

Example 1

One thousand hard gelatin capsules available from Eli Lilly & Co. (size 0) were each filled with 50 mg of micronized candidin (200% activity) obtained from S.B. Penick & Co., 200 mg calcium carbonate, 50 mg potassium phosphate (monobasic) and sufficient lactose to bring each capsule to full volume (i.e. about 80 to 100 mg lactose). In preparing the formulation for filling the capsules all of the above-identified materials were passed through a #60 mesh sieve. The mixing of the materials was initially carried out in container or the like using a paddle to stir the materials. After all the materials for the thousand capsules had been mixed together, the contents of the container was placed in a blender and mixing was continued for about two hours to achieve a homogeneous formulation. Each capsule was then filled with this admixture to provide the quantity of each ingredient indicated, supra.

Example 2

One thousand capsules containing enteric coated beadlets using candidin as the active ingredient, were prepared as follows: The quantities of candidin, calcium carbonate, potassium phosphate (monobasic) and lactose were blended together as described in Example 1. In this case, 60.5 gms (by activity) of candidin (S. B. Penick & Co.), 220 gms calcium carbonate and 55 gms potassium phosphate (monobasic) were passed through a #60 mesh sieve and the contents of the sieve receptacle transferred to a blender. The resulting

- sufficient number of nonpareil seeds placed blended powder was then coated onto a in a coating pan (e.g. 10-12 micron size) using a 270 ml solution (divided into nine equal parts) of 50 ml shellac solution (5%) 10 gms polyvinyl pyrrolidone ("Plasdone 29-32" "PLASDONE" is a registered Trade Mark) and 300 ml ethyl alcohol for adhering the formulation to the nonpareil seeds.
- 10 This procedure was carried out by spraying 30 ml of this solution (using an atomizer) with a continuous rotation of the pan and adding 37.37 gms blended powder. Rotation of the pan is continued until the alcohol has evaporated. This procedure is repeated nine times to provide nine coats of candicidin around the nonpareil seeds. Thereafter 50 ml of a solution of shellac and ethyl alcohol are sprayed over the coated seeds with continuous rotation of the pan and the seeds are air dried.

- The air dried seeds are placed in a clean coating pan and coated with 440 ml of a solution (divided into twenty equal parts) made up of 37.5 grams cellulose acetate phthalate, 150ml acetone, 212.5 ml ethyl alcohol, 9.37 ml diethyl phthalate and 118.75 ml methylene chloride, using 5 lbs. air pressure to spray. The coated seeds are air dried (room temperature) with continuous rotation of the pan. This procedure is repeated twenty times so that all 440 ml of the cellulose acetate phthalate solution is used. The coated seeds are then passed through a #12 mesh sieve, discarding any oversize. Then the seeds are passed through a #16 mesh sieve discarding the undersize. Capsules as described in Example 1 are then filled with the remaining coated seeds ranging in size from about 1200 to 1700 microns.

Example 3

- One thousand hard gelatin capsules available from Eli Lilly & Co. (size 0) were each filled with 50 mg micronized candicidin, 210 mg. lactose (USP), 90 mg glycine (USP) and 210 mg calcium carbonate (heavy USP). The candicidin, glycine and calcium carbonate were triturated together in a pestle and mortar until a very fine powder was obtained and then the lactose was added to this powder. Each capsule was then filled with this admixture to provide the quantity of each ingredient indicated above. Obviously, the quantity of active ingredient may be altered in each capsule as desired.

Example 4

- Eight thousand capsules containing candicidin as the active ingredient were prepared using 440 gm (by activity) of candicidin, 400 gm potassium phosphate monobasic (USP), 1600 gm calcium car-

bonate heavy (USP) and 1840 gm nonpareil seeds (1000 to 1200 microns). The nonpareil seeds are placed in a coating pan and sprayed with 220 ml of a shellac solution (hereinafter shellac solution "A") made up of a 80 gm shellac solution (6 lb. cut in solution) diluted with 280 gm anhydrous alcohol (using an atomizer and 5 lbs. air pressure) with a continuous rotation of the pan until the seeds are completely wet. Thereafter about 1/10 of the powder blend (291 gm) obtained by mixing the candicidin, calcium carbonate and potassium phosphate is slowly added to the pan, the pan being rotated until the powder completely adheres to the seeds. Additional ethyl alcohol is added to the pan to insure complete adherence of the powder onto the seeds and rotation is continued until the alcohol has been evaporated.

Following the foregoing coating operation there is sprayed onto the seeds with an atomizer using 5 lb. air pressure about 196 ml of a solution made up of 192 gms. shellac solution 120 grams polyvinylpyrrolidone and 1768 ml ethyl alcohol with continuous rotation of the pan until the seeds are completely rewet. The atomizer is then stopped and there is slowly added 1/10 of the powder blend of candicidin, calcium carbonate and potassium phosphate and rotation is continued until the powder completely adheres to the seeds. Thereafter ethyl alcohol is added to complete adherence of the powder to the seeds and the alcohol is evaporated. This coating process is repeated eight more times.

After the eight additional coats, have been added, 220 ml of shellac solution "A" is sprayed onto the coated seeds using 5 lb. pressure with a continuous rotation of the pan until the solution is used up and the alcohol evaporated. The coated seeds are permitted to air dry and are then sieved through a #12 mesh sieve and the oversize seeds discarded. Then sieve the seeds through #16 mesh sieve the undersize seeds being discarded. Capsules as described in Example 1 are then filled with the remaining coated seeds having a size between about 1200 to 1700 microns to provide 50 mg of candicidin (by activity) per capsule.

The polyenic macrolides described herein are useful in treating prostate hypertrophy, hypercholesterolemia in mammals weighing at least one kilogram (e.g. dogs and humans). These uses have been described in the aforementioned copending application Serial Nos. 623,847, & 627,313 and described in various literature publications subsequent to the filing of such applications. In view of the fact that the polyene macrolides bind with cholesterol

- in the intestinal tract and prevent absorption of cholesterol they are useful in dietary control and in treatment of conditions where it is desirable to control the quantity of cholesterol absorbed into the blood stream. The polyenic macrolides also exhibit anti-androgen activity and are useful for treating conditions associated with androgen disorders, (e.g. acne).
- 10 The daily effective dose of the polyenic macrolide depends upon the condition being treated, the individual characteristics of each mammal being treated as well as the particular polyenic macrolide being used. Generally, the dose range is from about 1 mg to about 40 mg per kilogram of body weight per day for the treatment of prostate hypertrophy and hypercholesterolemia. To prevent absorption of cholesterol a daily dose of between 1 mg to 15 mg per kg of body weight is effective whereas in treating androgen disorders the effective dose generally requires a minimum of 1 mg per kg of body weight. Clinical tests with candidin have been effectively carried out to treat prostatic hypertrophy using a daily dose of between 2 and 10 mg. per kg. of body weight per day.
- 30 WHAT WE CLAIM IS:—
1. A capsule which contains a multiplicity of beadlets (as herein defined) each containing a composition comprising (i) a polyenic macrolide and (ii) an absorbent material capable of binding the polyenic macrolide under acidic conditions and releasing the polyenic macrolide under substantially neutral conditions, the weight ratio (i):(ii) being from 1:2 to 1:8.
 2. A capsule according to claim 1 wherein the polyenic macrolide comprises a hexaene or heptaene macrolide.
 3. A capsule according to claim 2 wherein the polyenic macrolide is candidin.
 4. A capsule according to claim 2 wherein the polyenic macrolide is fungimycin.
 5. A capsule according to claim 2 wherein the polyenic macrolide is hamycin.
 6. A capsule according to claim 2 wherein the polyenic macrolide is medio-cidin.
 7. A capsule according to any preceding claim wherein the weight of polyenic macrolide present is from 25 mg. to 100 mg.
 8. A capsule according to any preceding claim wherein the absorbent material is capable of binding the polyenic macrolide at a pH from 3 to 5.
 9. A capsule according to any preceding claim wherein the absorbent material is capable of releasing the polyenic macrolide at a pH from 6 to 7.
 10. A capsule according to any preceding claim wherein the absorbent material is an inorganic salt or base of a di- or tri-valent metal.
 11. A capsule according to claim 10 wherein the di- or tri-valent metal is magnesium, calcium, aluminium, bismuth or iron.
 12. A capsule according to claim 10 or 11 wherein the inorganic salt or base is a sulphate, silicate, phosphate, carbonate or hydroxide.
 13. A capsule according to any of claims 1 to 9 wherein the absorbent material is a cellulose derivative, a starch, a pectin, a gum or an ion-exchange resin.
 14. A capsule according to any preceding claim wherein an acid material is present for maintaining the pH of the composition between 6.5 and 7.5.
 15. A capsule according to any preceding claim wherein the beadlets are provided with a sustained release coating.
 16. A capsule according to claim 15 wherein the coating is an enteric coating.
 17. A capsule according to claim 15 wherein the coating is a shell of hard gelatin.
 18. A capsule according to any preceding claim containing potassium phosphate.
 19. A capsule which contains a multiplicity of beadlets (as herein defined) each containing a composition comprising (i) candidin and (ii) calcium carbonate, the weight ratio (i):(ii) being from 1:2 to 1:8, wherein the weight of (i) in the composition is from 25 mg. to 100mg., the weight of (ii) in the composition is from 50 mg to 400 mg and the pH of the composition is between 6.5 and 7.5.
 20. A capsule according to claim 1 substantially as hereinbefore described with reference to the Examples.
 21. A process for producing a capsule according to any preceding claim, which process comprises blending (i) a polyenic macrolide with (ii) an absorbent material capable of binding the polyenic macrolide under acidic conditions and releasing the polyenic macrolide under substantially neutral conditions such that the weight ratio (i):(ii) is from 1:2 to 1:8; preparing a multiplicity of beadlets (as herein defined) from the composition so produced; and encapsulating the multiplicity of beadlets so produced to form a dosage unit.
 22. A process according to claim 21 wherein the dosage unit so formed contains an amount of polyenic macrolide effective to deposit from 1 mg. to 40 mg. of macrolide per kilogram of a host's body weight per day.
 23. A process according to claim 21

substantially as hereinbefore described with reference to the Examples.

24. A capsule whenever prepared by a process according to any of claims 21 to 5 23.

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Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd., Berwick-upon-Tweed, 1974.
Published at the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

SPECIFICATION NO 1375986

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of SCHMID LABORATORIES INC., a Corporation organised and existing under the laws of the State of New Jersey, United States of America, of Route 46 West, Little Falls, New Jersey, United States of America.

THE PATENT OFFICE

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